L15 ANSWER 2 OF 14 MEDLINE DUPLICATE 1

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AB When utilized as a macromolecular drug targeting ligand, folic acid (Pte-Glu) has traditionally been coupled to peptides, proteins and lipids via one of its two carboxylate groups fortuitously located within a distal **glutamyl** moiety. It has been assumed in the literature that the **gamma-glutamyl** carboxylate of Pte-Glu is the preferred **conjugation** site for macromolecules enduring endocytosis via the **folate**-binding protein receptor. However, it is also possible that the steric placement of the attached macromolecule around the vitamin's pteridine moiety may be the more influential parameter controlling this delivery mechanism. Using solid-phase chemistries, we have synthesized dipeptide derivatives of pteroic acid for the purpose of identifying the preferred site onto which a macromolecule can be chemically attached without compromising its endocytosis potential. Thus, using fluorescent and radiolabeled **conjugates**, we have determined that macromolecules attached to Pte-Glu by either an **alpha**- or **gamma-glutamyl** linkage could associate with receptor-bearing cells at virtually identical levels. We further discovered that removal of the remaining un-**conjugated** **glutamyl** carboxylate had no inhibitory effect on cell uptake; and, the cytotoxicity of related momordin toxin **conjugates** were comparable among the various pteroate derivatives tested. From these observations we suggest that the preparation of endocytosis-competent pteroate-macromolecule **conjugates** is strongly influenced by the steric environment around the ligand's para-aminobenzoic acid moiety, and that no selective isomeric (i.e. alphaGlu versus gammaGlu) **conjugation** requirement necessarily exists.